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EDITORIAL

Network meta-analysis of antiplatelet treatments for secondary stroke prevention

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This editorial refers to 'Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke'† by V. Thijs *et al.*, on page 1086

Network meta-analysis is a fairly new method for assessing the relative effectiveness of two treatments when they have not been directly evaluated in a controlled randomized trial (CRT) but have each been compared with other treatments.[1] It allows an estimation of the heterogeneous effect of any given treatment and for inconsistency in the evidence from different pairs of treatments.[1] It has also been used to compare the efficacy of different therapies, such as the effect of antihypertensive drugs on health care outcomes[2] and on the incidence of diabetes mellitus,[3] of antithrombotic treatment on stroke prevention in non-rheumatic atrial fibrillation,[4] and of drug-eluting and bare-metal stents on outcome.[5]

The efficacy of antiplatelet agents in secondary stroke prevention has been investigated in CRTs comparing one antiplatelet agent with another and with a placebo, and a combination of two antiplatelet agents with a placebo and with another antiplatelet drug. Aspirin,[6] ticlopidine,[7] and dipyridamole and aspirin plus dipyridamole[8] have been shown to be more effective than placebo alone. In contrast, a comparison of ticlopidine with aspirin produced contradictory results.[9–11] A *post hoc* subgroup analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study showed no advantage of clopidogrel compared with aspirin alone in secondary stroke prevention.[12] However, CAPRIE was not set up for detecting significant differences in this subgroup.[12] The combination of aspirin and clopidogrel was not more effective than either aspirin alone[13] or clopidogrel alone.[14] In contrast, the European Stroke Prevention Study 2 (ESPS)[8] and a meta-analysis[15] have reported that aspirin plus dipyridamole is more effective than placebo, aspirin, or dipyridamole. The aspirin dose used in ESPS 2 (50 mg/day),[8] and in ~50% of the patients of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT; 30–50 mg/day),[15] was <75 mg/day, which was not more effective than placebo in the meta-analysis of the Antithrombotic Trialists' Collaboration.[6] These findings indicate that further studies and/or analyses, which compare the aforementioned antithrombotic treatments, in particular aspirin plus dipyridamole with aspirin ≥75 mg/day and clopidogrel, are needed. Thijs *et al.*[16] have addressed most of these questions using network meta-analysis. The authors compared the efficacy of antiplatelet agents and combinations of such agents (aspirin, aspirin plus dipyridamole, the thienopyridines ticlopidine and clopidogrel, and the combination of aspirin and thienopyridines) in the prevention of serious vascular events after stroke and transient ischaemic attacks (TIAs). As expected, all antiplatelet regimens were more effective than placebo, and aspirin plus dipyridamole was more effective than aspirin alone.[16] Interestingly, the combination of aspirin with dipyridamole was also more effective than the thienopyridines (odds ratio, 0.84; 95% confidence interval, 0.73–0.97).[16]

Network meta-analysis has been criticized, because it may combine evidence from trials that are substantially different in design.[17] Another limitation is the reliance on random effect methods for meta-analyses, which allow smaller studies a greater effect. Thereby, a small outlying trial can have undue influence. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial uses a 2 × 2 factorial design to compare the efficacy of aspirin plus dipyridamole with clopidogrel, and telmisartan with placebo for secondary stroke prevention in >20 000 patients with ischaemic stroke.[18] The ProFESS trial will allow the validity of the network meta-analysis of Thijs *et al.*[16] to be evaluated.

Conflict of interest: none declared.

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